Remarks

Claims 1, 4-11, and 13-30 are pending and under examination. By this amendment claim 5 is currently amended; no claims are canceled; and no new claims are added. No new subject matter is introduced.

Claim 5 is currently amended to substitute "atopic dermatitis" for "allergic dermatitis".

Provisional Obviousness-Type Double Patenting Rejection

The Examiner indicates that instant claims 1, 4-11, and 13-30 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 19 of copending Application No. 10/817,165. The Examiner asserts that the claims are not patentably distinct from each other because they both claim and disclose methods of treating dermatitis or allergic reactions comprising administering to the subject a composition comprising an immunostimulatory oligonucleotide or immunostimulatory [oligonucleotide] and allergen.

Applicant in response is willing to consider filing a terminal disclaimer, if necessary, at the time that claims are deemed to be otherwise in condition for allowance. Applicant notes that both the instant application and Application No. 10/817,165, which is a divisional of the instant application, currently claim priority to the same parent application, filed July 15, 1994.

Rejections Under 35 U.S.C. § 112, first paragraph

The Examiner indicates that claims 1, 4-11, and 13-30 are rejected under 35 U.S.C. § 112, first paragraph, for alleged lack of enablement. More specifically, the Examiner asserts on page 4 that the enabled method for treating asthma (murine model) comprising administering to a subject in need of such treatment an immunostimulatory oligonucleotide (8-100 nucleotides long) comprising SEQ ID NO:10 does not reasonably provide enablement for the ability to treat atopic dermatitis or allergic dermatitis comprising administering to a subject in need of such treatment any immunostimulatory oligonucleotide (8-100 nucleotides long) having the claimed

formula as shown in claims 1 or 5, or the broad scope of the possible CpG-ODN that are envisioned in the formulas of claims 1 or 5. The Examiner goes on to assert on page 5 that the results shown for asthma do not indicate that the CpG will function in the same manner to treat atopic dermatitis or allergic dermatitis. On page 7 the Examiner asserts that one skilled in the art would not accept on its face the examples given in the specification as being correlative or representative of the successful treatment of atopic dermatitis or allergic dermatitis in any organism comprising the administration by any route of any immunostimulatory nucleic acid comprising the formulas in claims 1 and 5 in view of the lack of guidance in the specification and known unpredictability associated with the ability to predict the biological effects exerted by CpG containing oligonucleotides in any and/or all organisms. On page 8 the Examiner goes on to assert that no correlation is taught in the instant disclosure between the ability of these CpG containing oligonucleotides to induce a Th1 response in vitro (e.g., amount of IL-6 induction) and their ability to treat a representative number of atopic conditions (i.e., atopic dermatitis or allergic dermatitis) in vivo. Finally, the Examiner asserts on page 8 that an assumed common mechanism of action does not ensure enablement for treatment.

As noted above, claim 5 is currently amended to substitute "atopic dermatitis" for "allergic dermatitis". For reasons set forth below, Applicant respectfully disagrees and requests the Examiner to reconsider and withdraw her rejection under 35 U.S.C. § 112, first paragraph.

The claims as currently amended all relate to methods for the treatment of atopic dermatitis. Applicant submits that atopic dermatitis is recognized by those skilled in the art to be a major form of eczema that is distinct from allergic contact dermatitis (ACD). For example, ACD is believed to be mediated primarily by CD8+ cytotoxic T cells in a Type IV delayed-type hypersensitivity reaction. Akiba H et al. (2004) *J Invest Dermatol* 123:488-93 (cited by Examiner in the office action). In contrast, atopic dermatitis is believed to represent primarily a (CD4+) Th2-related disorder characterized by increased IgE levels, eosinophilia, and IL-4- and IL-5-secreting Th2-type cells in the peripheral blood and Th2-skewed cytokine gene expression and eosinophilia in skin lesions, particularly acute skin lesions. Leung DYM (1999) *J Allergy Clin Immunol* 104:S99-108 (cited by the Examiner in the office action). The examples of

exacerbation of 2,4-dinitrofluorobenzene (DNFB)-induced ACD by local (but not systemic) injection of CpG ODN described in Akiba H et al. (*supra*) and Satoh M et al. (same group, abstract cited by Examiner in the office action), are thus not relevant to the claims because they relate to ACD rather than to atopic dermatitis.

Applicant respectfully disagrees with assertions made by the Examiner that the results shown for asthma do not indicate that the CpG will function in same manner to treat atopic dermatitis or allergic dermatitis and that an assumed common mechanism of action does not ensure enablement for treatment. As has already amply been made of record, Applicant believes that a common mechanism of disease, as well as a common mechanism of action of CpG-containing immunostimulatory oligonucleotides to treat the underlying common mechanism of the disease, are compelling evidence that the results shown for asthma do indicate that CpG oligonucleotides can be used to treat atopic dermatitis as claimed.

Specifically, Applicant has described a class of molecules (oligonucleotides) having a common structural motif (a CpG dinucleotide) that when administered to a subject result in an aspect of the immune response being altered, with a Th1 response being favored. This class of oligonucleotides is described throughout the specification, and their ability to produce a Th1-favored immune response is not only described but data is presented in vitro and in vivo using a number of different CpG-containing oligonucleotides. For instance, Table 5 on page 27 of the specification shows induction of Th1 cytokines using several different oligonucleotides.

It is now believed that CpG oligonucleotides act through a common cellular receptor, Toll-like receptor 9 (TLR9). It is believed that CpG oligonucleotides are recognized by TLR9 and that this interaction leads to the promotion of an immune response in which a Th1 response is favored. Hemmi H et al. (2000) *Nature* 408:740-45 was one of the first publications to describe the role of TLR9 in activation of the immune response by CpG oligonucleotides. A copy of this reference is provided for the Examiner with the IDS filed herewith. Briefly, Hemmi et al. describes studies in a TLR9 knockout mouse. The CpG-mediated Th1 immune response was abolished in these mice, confirming the role of TLR9 in CpG-mediated signaling. It is also

now believed that receptors for TLR9 are expressed by a number of types of immune cells, including circulating immune cells. Therefore delivery of CpG to immune cells expressing TLR9 receptors, for example by either local or systemic administration, is believed to be effective for inducing TLR9 signaling and an attendant Th1-favored immune response.

Even if the Examiner were to reject the foregoing as evidence sufficient to show enablement, Applicant respectfully wishes to call to the attention of the current examiner the Declaration Under 37 C.F.R. 1.132 of co-inventor Joel Kline, submitted on September 10, 2003. This declaration sets forth original experimental data showing that CpG oligonucleotides were effective in the treatment of atopic dermatitis in a mouse model. Specifically, mice treated with intraperitoneal (i.e., systemic) injections of CpG-ODN 1826 (corresponding to SEQ ID NO:10 in the instant application) dramatically reduced skin eosinophilia as compared to control animals not treated with CpG. In addition, the experiments described in the declaration specifically demonstrate that treatment with CpG-ODN 1826 was effective in treating both asthma and atopic dermatitis. Thus the results shown for asthma do indicate that CpG oligonucleotides effective for treating asthma also function to treat atopic dermatitis and that a common mechanism of action strongly supports enablement for the claimed method for treatment of atopic dermatitis.

On page 5 the Examiner makes reference to a number of publications for the proposition that the state of the art is unpredictable with regard to treatments using CpG. Applicant respectfully submits that, while some experimentation may be necessary to optimize the claimed methods, the claims nevertheless are adequately enabled. The test for enablement is not that no amount of experimentation is required in order to practice the invention, but rather that no undue amount of experimentation is required. As the specification and claims make clear, important features of the CpG oligonucleotides useful in the claimed methods include but a few, namely, a CpG dinucleotide wherein the C of the CpG dinucleotide is unmethylated, at least a minimal amount of flanking sequence, and a length of at least 8 nucleotides. The arguments above in respect of the mechanism of action of CpG-ODN and TLR9 as a receptor notwithstanding, in the context of this assertion of unpredictability it is respectfully submitted that the cited statement on page 461 of Weiner G (2000) *J Leukoc Biol* 68:455-63 ("we still do not understand the molecular

mechanisms responsible for the immunostimulatory effects of CpG DNA") is not relevant. It is not relevant because knowledge of the molecular mechanisms is not required in order for the claims to be enabled. Beyond the few key structural features of CpG oligonucleotides enumerated above, it is respectfully submitted that only a little, if any, amount of experimentation is needed to enable the full scope of the claims; additional experimentation beyond that amount may be viewed as efforts directed toward optimization, not enablement. Such optimization is not required to fulfill the enablement requirement.

Furthermore, the specification itself provides teaching in respect of certain preferred CpG motifs, including species-specific preferred CpG motifs. It was recognized at the time the invention was made, for example, that certain CpG motifs were better for activating murine cells than human cells, and vice-versa. See, for example, the paragraph bridging pages 27-28 of the specification.

On page 7 the Examiner asserts that the amount of direction or guidance presented in the specification and the presence or absence of working examples is a hindrance to practicing the claimed invention. As noted above, as well as already made of record, Applicant is of the view that the description and examples, both in vitro and in vivo, disclosed in the specification provide a sufficient amount of direction or guidance to practice the claimed invention. For example, particularly given the role and distribution of TLR9, a receptor for CpG, it is submitted that administration by any disclosed route of administration ("by any mode allowing the oligonucleotide to be taken up by the appropriate target cells (e.g., B cells and monocytic cells)", see page 42, paragraph beginning at line 5) is enabled. More specifically, such routes of administration can include, for example, oral, transdermal, subcutaneous, intravenous, parenteral, and intraperitoneal. *Ibid.* In respect of the Examiner's apparent concern about claims being drawn to "any and/or all organisms", Applicant points out that the term "subject" is disclosed on page 17 of the specification to refer to a human or vertebrate animal, and not just any and/or all organisms.

In view of the foregoing, Applicant respectfully requests reconsideration and withdrawal of the rejection of claims 1, 4-11, and 13-30 under 35 U.S.C. § 112, first paragraph.

Summary

Claim 5 is currently amended and arguments are advanced to overcome the rejection of claims 1, 4-11, and 13-30 under 35 U.S.C. § 112, first paragraph.

Applicant believes the claims are in condition for allowance. An early and favorable response is requested. If the Examiner believes that the application is not in condition for allowance, the Examiner is requested to call the Applicant's attorney at the telephone number listed below, prior to issuing an office action.

Respectfully submitted,
Krieg et al., *Applicant*

By: _____

Alan W. Steele, M.D., Ph.D., Reg. No. 45,128
Wolf, Greenfield & Sacks, P.C.
600 Atlantic Avenue
Boston, Massachusetts 02210-2211
Telephone: (617) 646-8000

Docket No. C1039.70048US00
Date: May 17, 2005
x05/17/05x